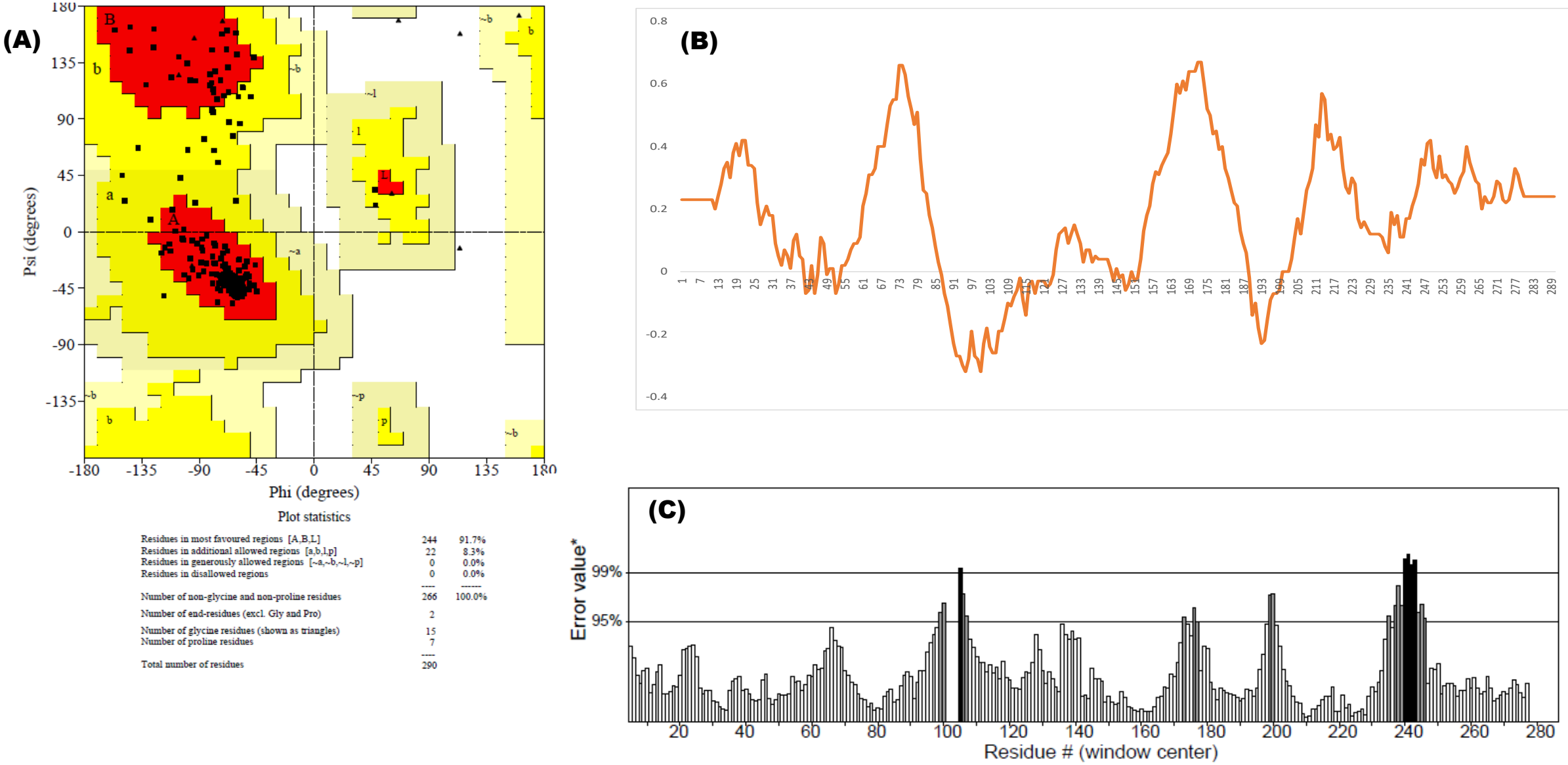


Figure S1. Validation of NSP6 Model through SAVES v5.0 server. (A) Ramachandran plot generated through PROCHECK server. (B) Structure validation with Verify-3D, and (C) ERRAT tool.

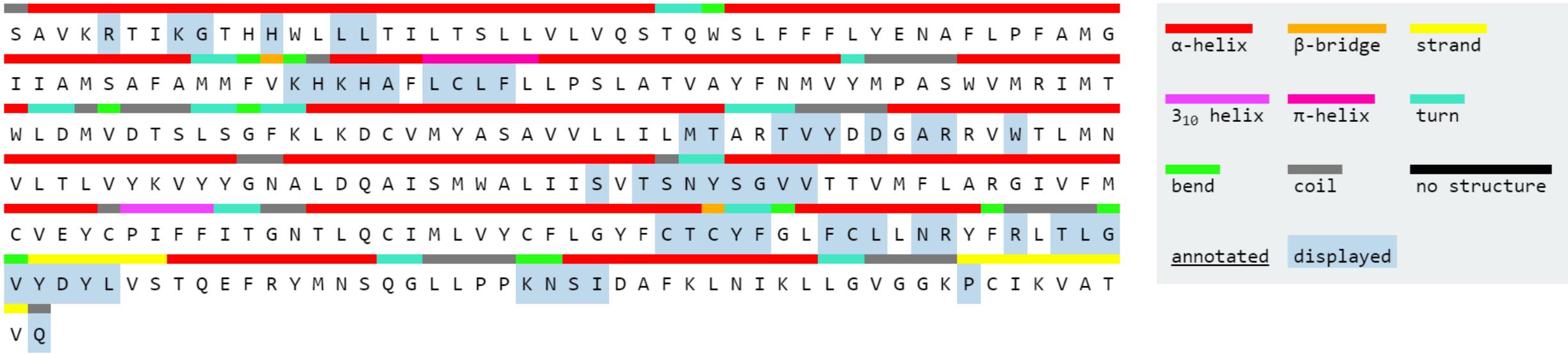
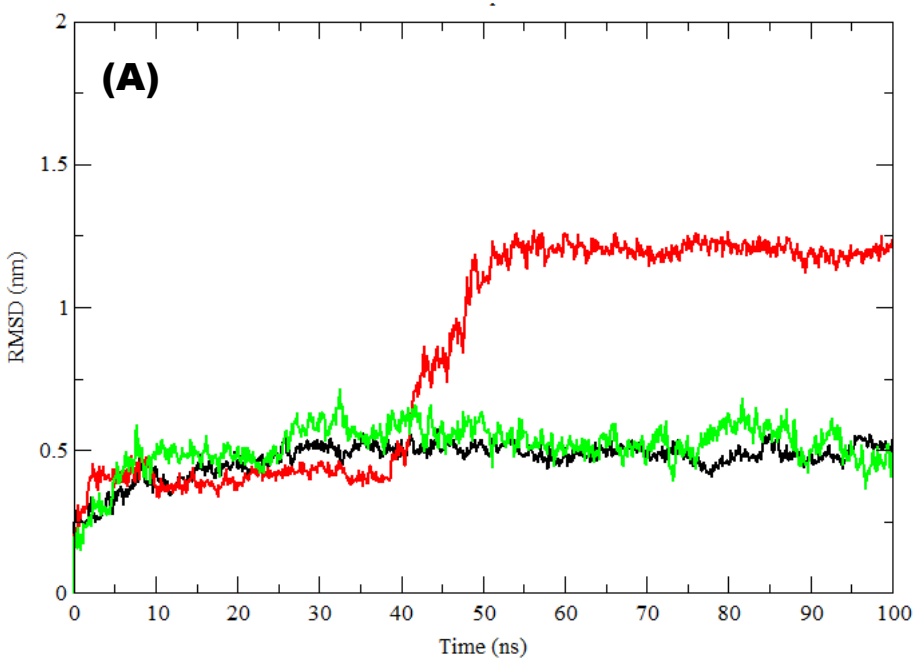
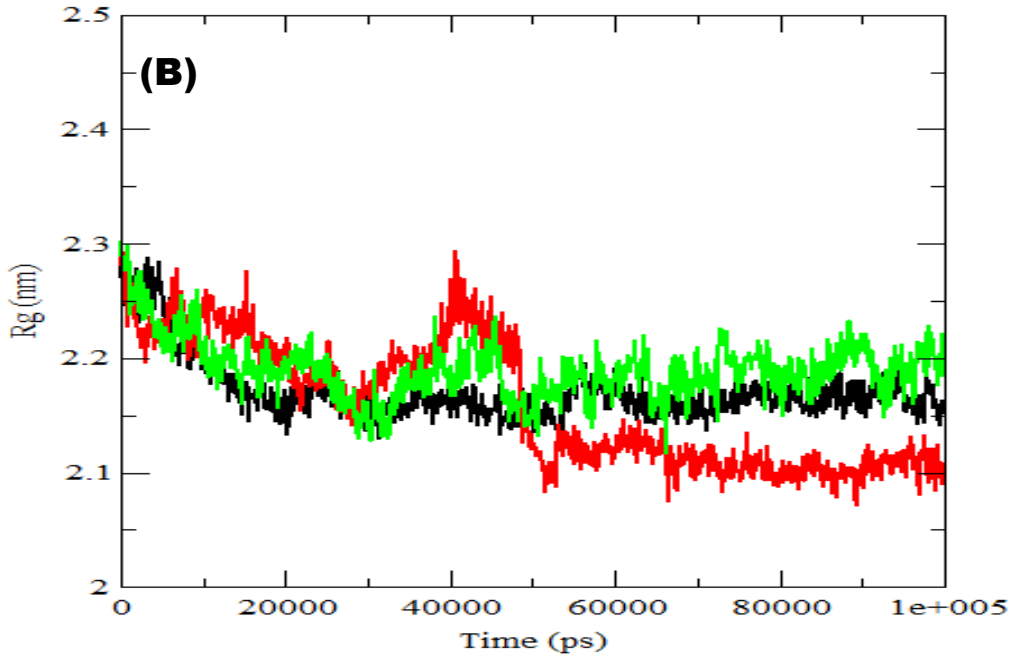


Figure S2. Binding pocket prediction through CASTp. The sequence of NSP6 along with their secondary structure annotation. The residues predicted to be in binding pocket is highlighted in light blue.





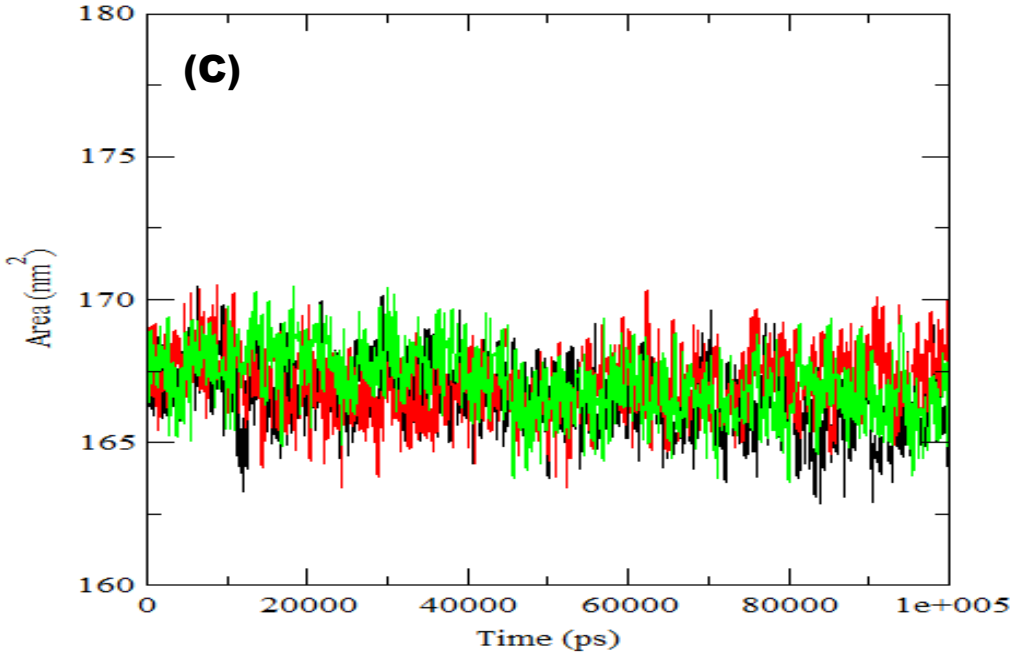


Figure S3. Conformational and dynamical analysis of NSP6 systems through all-atom molecular dynamics simulations. (A) RMSD of the Cα backbone of NSP6 (black), NSP6-Halperidol (green), and NSP6-Dextromethorphan (red) over 100 ns. (B) R*g* of residues during MD simulation for NSP6 (black), NSP6-Halperidol (green), and NSP6-Dextromethorphan (red) over 100 ns. (C) SASA during MD simulation for NSP6 (black), NSP6-Halperidol (green), and NSP6-Dextromethorphan (red) over 100 ns.

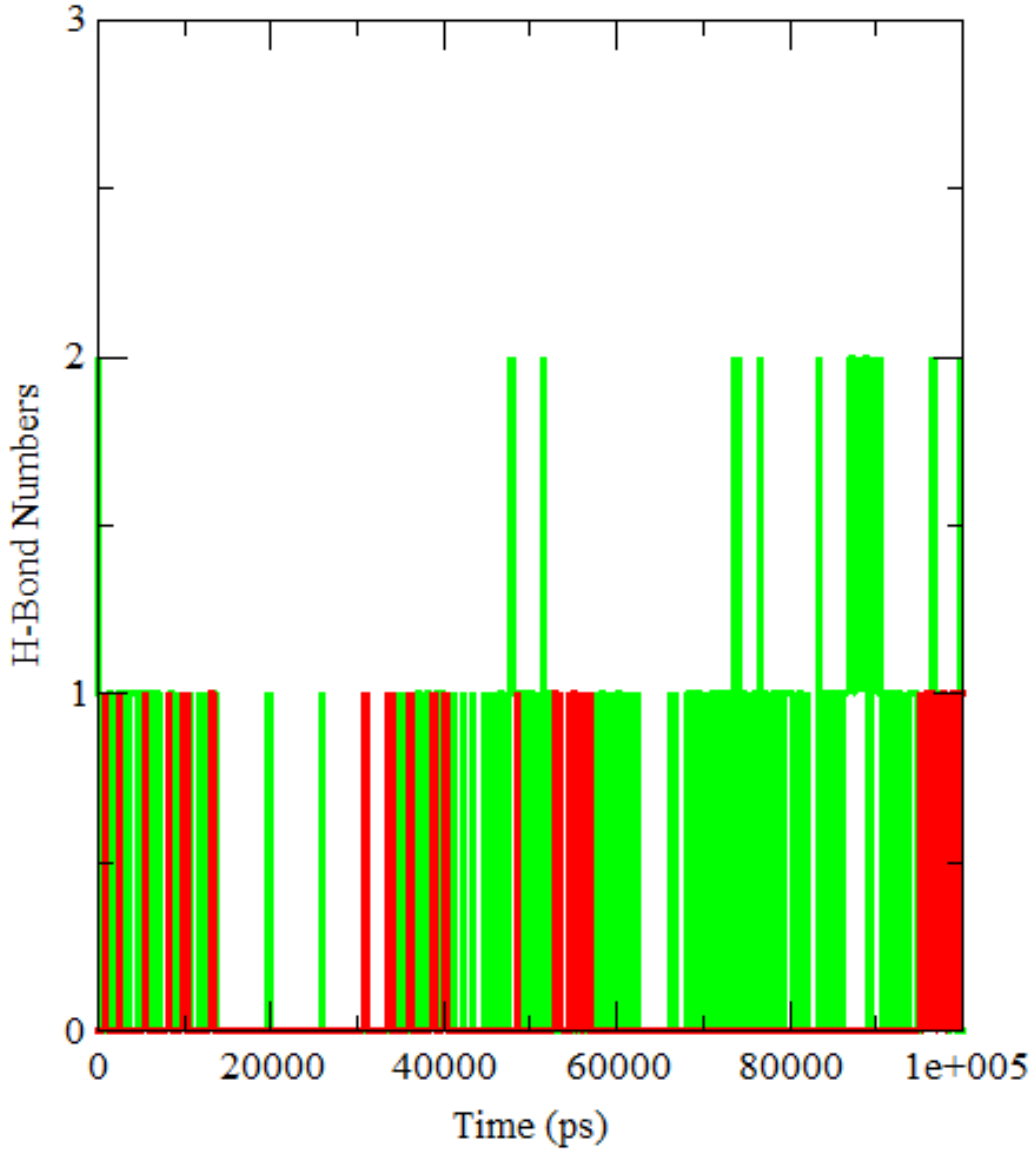


Figure S4. Number of hydrogen bond interactions formed between NSP6-halperidol (green) and NSP6-dextromethorphan (red) complexes during 100 ns simulation.

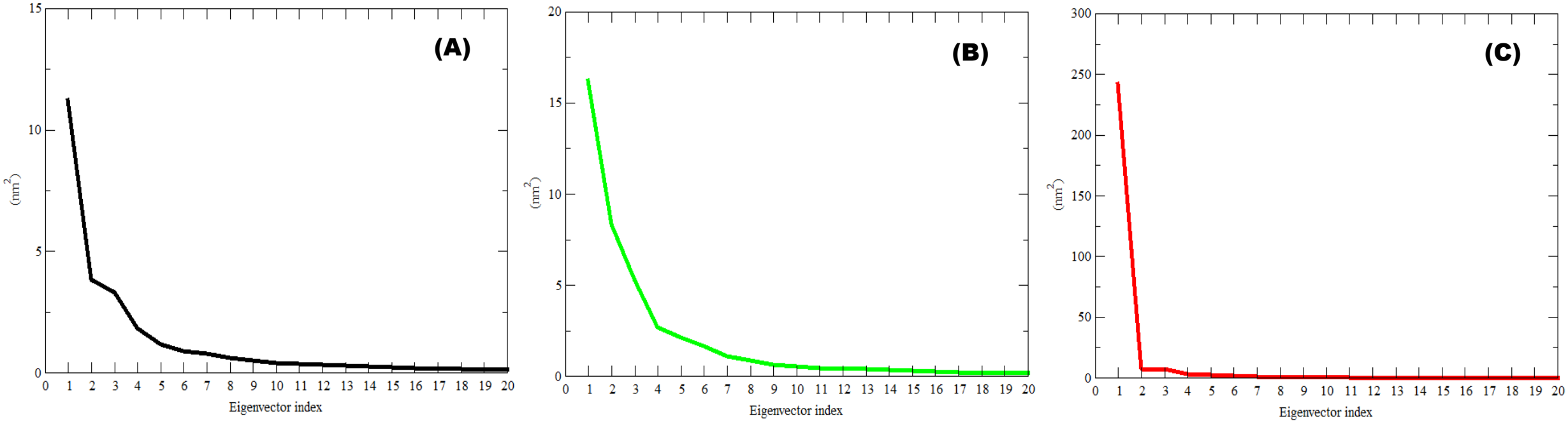


Figure S5. Principal component analysis. Plot of eigenvalues vs eigenvector index for the first 20 eigenvectors. (A) NSP6, (B) NSP6-Halperidol, and (C) NSP6-Dextromethorphan complexes.

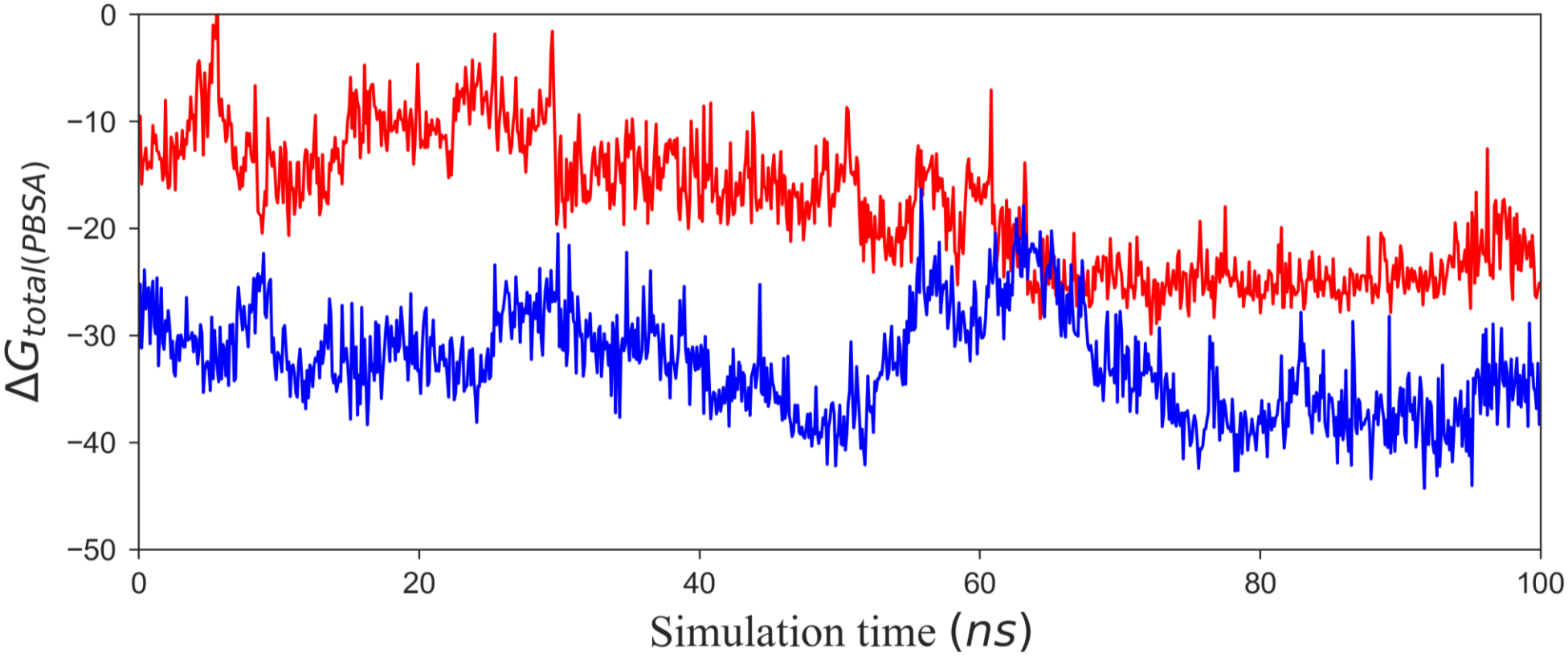


Figure S6. MM/PBSA results of drug binding. ΔG_{total} values of NSP6-haloperidol (blue) and NSP6-dextromethorphan (red) during the MD simulation.

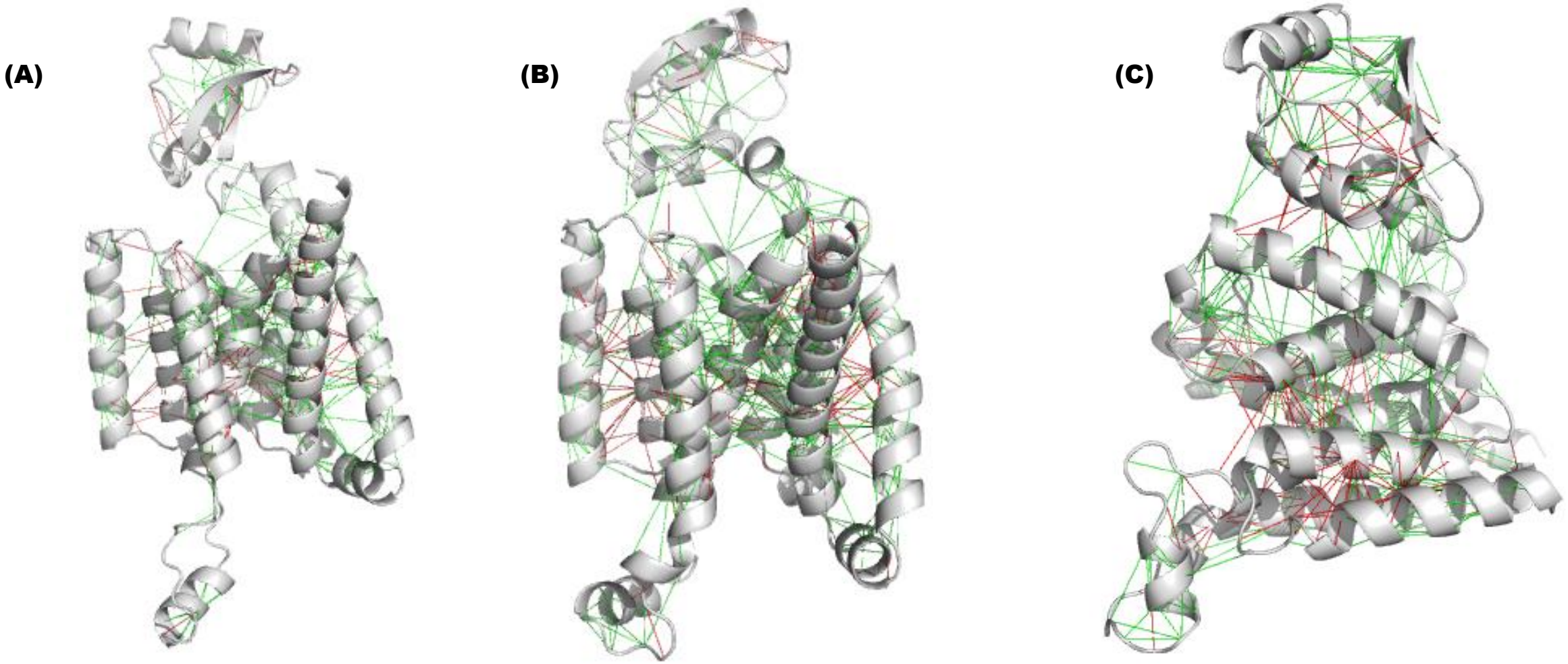


Figure S7. Drug binding induced frustration changes. Local frustration is depicted on the three-dimensional structures in (A) NSP6, (B) NSP6-Halperidol, and (C) NSP6-Dextromethorphan complexes. The large cluster of minimally frustrated interactions (green) defines the core of the protein, whereas highly frustrated interactions (red) occur on the surface of the protein.

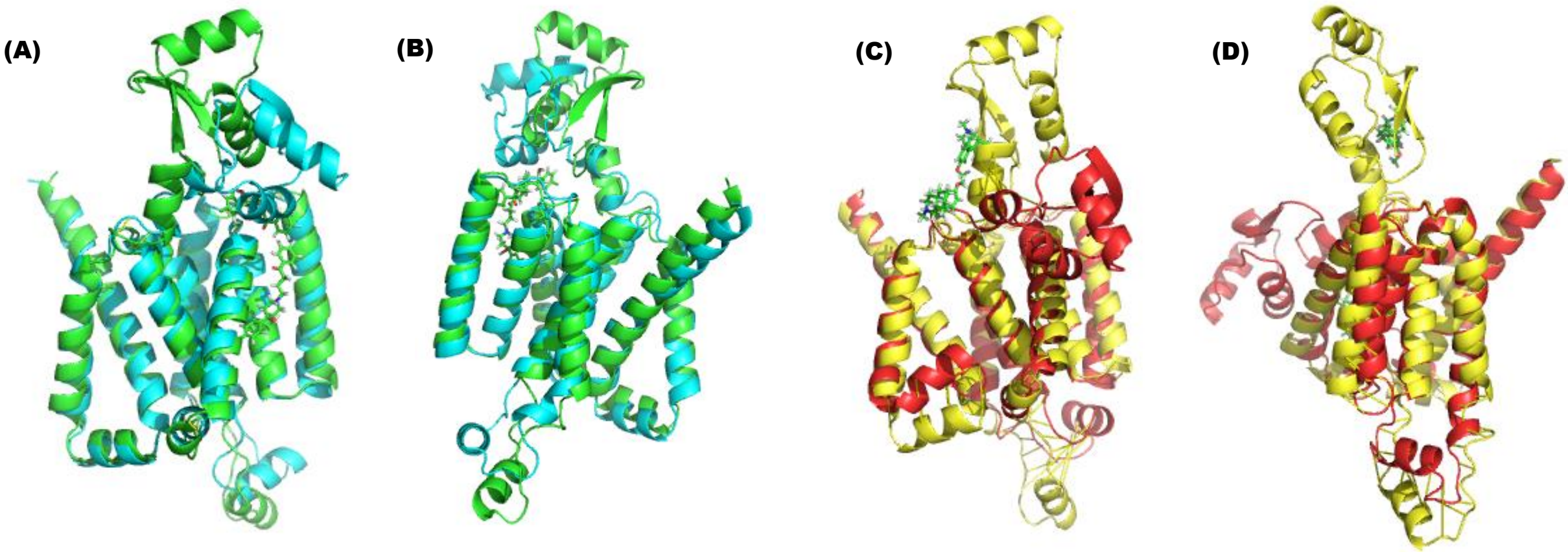


Figure S8. Structural comparison of haloperidol and dextromethorphan binding to NSP6. The structural representatives at two different periods (50ns, and 100ns) during the simulation are superimposed with unliganded NSP6 for comparison. The structural representatives for the most abundant structure for NSP6 in complex with haloperidol (green and cyan) and in complex with dextromethorphan (yellow and red) are superimposed for comparison. The superimposed structures for NSP6-haloperidol complex (A,50ns; B,100ns) and NSP6-dextromethorphan complex (C,50ns; D,100ns) are shown for comparison.

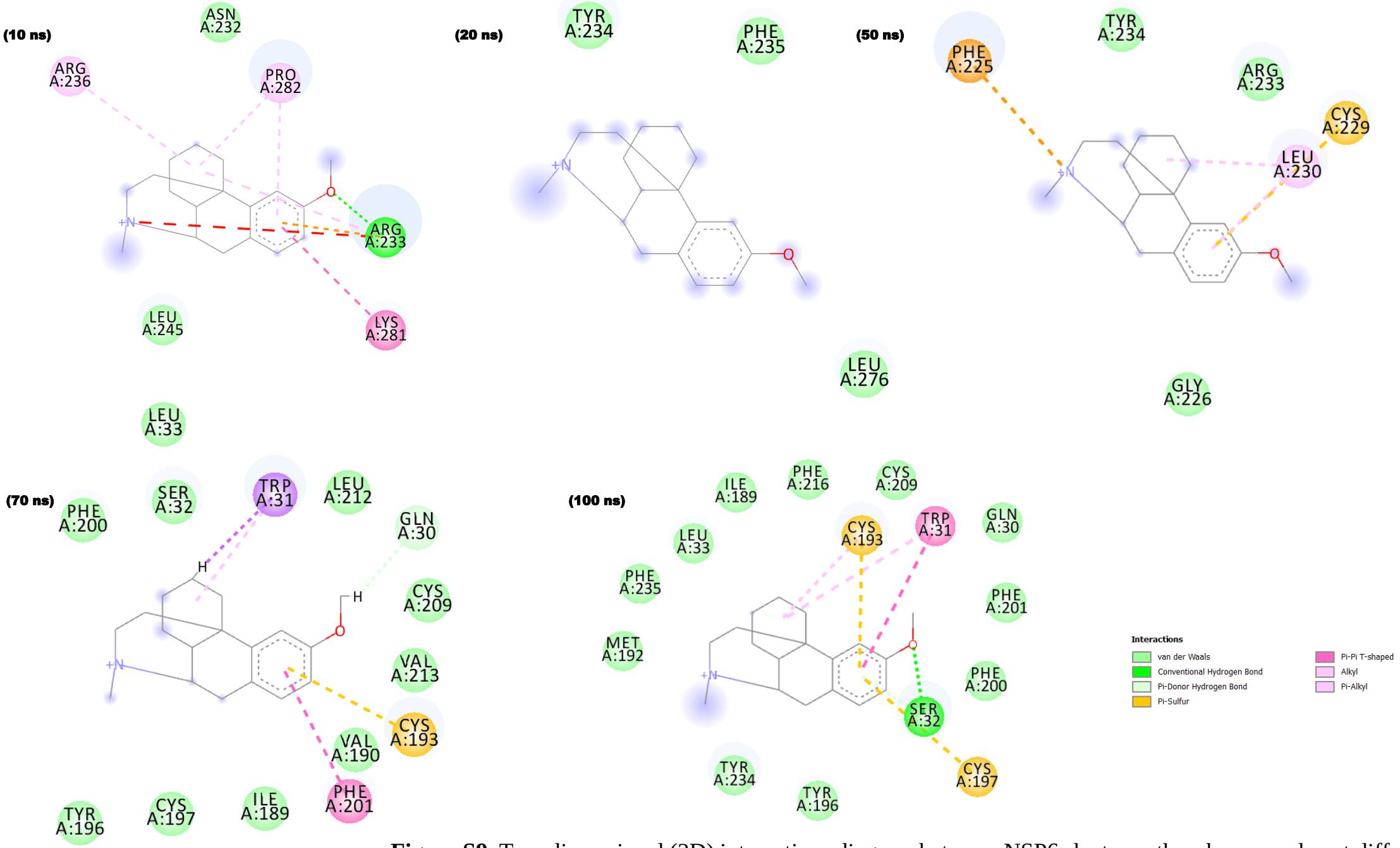


Figure S9. Two-dimensional (2D) interactions diagram between NSP6-dextromethorphan complex at different time points.

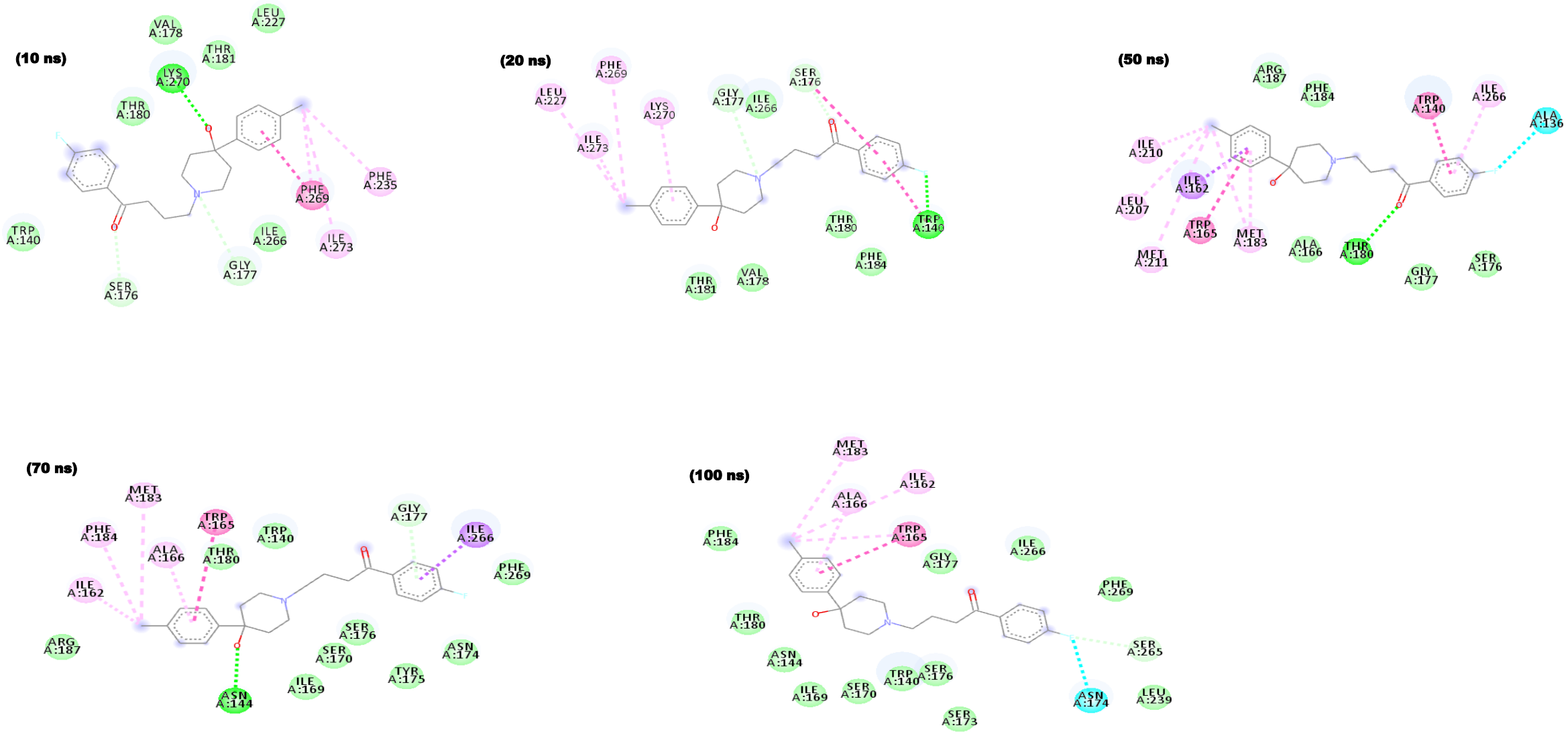


Figure S10. Two-dimensional (2D) structural representation of NSP6-haloperidol complex at various time points.